



HIV infection in refugees: a case–control analysis of refugees in Rhode Island

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Summary

Objectives: The number of HIV-infected refugees entering the USA is increasing. There is little data describing the HIV-infected refugee population and the challenges encountered when caring for them. We performed a retrospective case–control analysis of HIV-infected refugees in order to characterize their co-morbidities, baseline HIV characteristics, and longitudinal care compared to HIV-infected non-refugees.

Methods: A retrospective chart review was performed of HIV-infected refugees and non-refugees who were matched for gender, age, and time of establishment of initial HIV care.

Results: The refugee population studied was largely from West Africa. Refugees were more likely than non-refugees to have heterosexual risk for HIV infection, latent tuberculosis infection, and active hepatitis B. Refugees were less likely than non-refugees to have a history of substance use, start antiretrovirals, and be enrolled in a clinical study. The baseline CD4 counts and HIV plasma viral loads were similar between the two groups.

Conclusions: Clinicians caring for West African HIV-infected refugees should be knowledgeable about likely co-morbidities and the impact of cultural differences on HIV care. Further studies are needed to develop culturally competent HIV treatment, education, and prevention programs for refugees who are beginning a new life in the USA.

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Introduction

Prior to 1999, it was difficult for HIV-infected refugees to enter the USA. The US immigration policy demanded that HIV-infected refugees prove that their admittance to the USA would not result in costs to any governmental agency, unless

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that agency provided prior consent.¹ This policy was revised by the United States Citizenship and Immigration Services (USCIS) in 1999 making it no longer necessary for HIV-infected refugees to prove that they would not be a financial burden to government-funded programs.² Since that policy revision, 249 260 refugees gained entrance into the USA between 2000 and 2004, of whom 1085 (0.43%) were HIV-infected (K.A. Gauger, Department of State, Office of Admissions, personal communication).

A refugee is an individual who has fled their country of nationality for fear of persecution. Because refugees have migrated away from their home country under duress, they often have experienced difficult living conditions characterized by poor nutrition, poverty, overcrowding, and absence of healthcare infrastructure and immunization programs, and suffer from physical and psychological trauma. These destabilizing factors have been thought to increase the risk for HIV infection, which can be magnified by refugees having limited knowledge of HIV transmission and methods for prevention.^{3–5} Refugees are also at increased risk of other infectious and non-infectious co-morbidities including tuberculosis (TB), parasitic infections, viral hepatitis, and mental health disorders.^{3,6} The number of HIV-infected refugees entering the USA has been increasing since 1999, yet data describing this population and challenges faced in providing medical care are sparse. To date, there have been no comparative studies examining HIV-infected refugees and HIV-infected non-refugees.

Moreno et al. reviewed their experience in caring for 34 HIV-infected refugees.⁷ A history of torture was reported in the majority, and approximately one-half reported a history of malaria. Other co-morbidities reported included TB, parasites, and hepatitis B, and one-half were diagnosed with major depression and one-third with post-traumatic stress disorder (PTSD). One-quarter of the refugees studied met the definition for AIDS and almost one-half met indications for antiretroviral (ARV) therapy. The authors noted several challenges in caring for this population including difficulty discussing the topics of substance abuse, safe sex, and the indications for antiretroviral treatment.

There is little data on ARV utilization and outcomes for HIV-infected refugees. However, a study by Moreno et al. suggested that the refugees who were started on ARV therapy did well.⁷ There was a report of a recurrence of PTSD symptoms after initiation of efavirenz-containing ARV regimens in two refugee patients, which illustrates the unique challenges that may be encountered in caring for this population due to the frequency of mental health disorders.⁸

We provide comprehensive HIV care for the majority of HIV-infected refugees resettled in Rhode Island. Our Center is funded by the Ryan White C.A.R.E. Act, provides HIV care for approximately 1200 HIV-infected patients in southeastern New England, and is affiliated with the Alpert Medical School of Brown University. The overall racial/ethnic composition of patients receiving care at the center is: 19% Hispanic/Latino, 30% African-American, 48% white, and 19% more than one race. Women represent 36% and men represent 64% of patients. Care is provided to all HIV-infected persons referred to the center, regardless of ability to pay.

The objective of this study was to perform a retrospective case–control analysis that compared demographic and clinical data from HIV-infected refugees with HIV-infected non-

refugees to better characterize the refugee population with respect to HIV acquisition, disease co-morbidities, HIV stage upon establishment of care, ARV utilization, enrollment in clinical studies, and adherence with appointments. The goal was to provide a better understanding of the unique characteristics of the refugees and the clinical challenges that are encountered, and to help clinicians who are currently caring for HIV-infected refugees.

Materials and methods

Fifty-two HIV-infected persons classified as refugees according to the United Nations High Commissioner for Refugees, established care at our center between 2000 and 2006. Referral to our center was facilitated by a local refugee resettlement agency that works in conjunction with the United States Committee for Refugees and Immigrants. For the purposes of this study, each refugee was matched with an HIV-infected non-refugee of the same gender, using optimal variable matching on age and date of their initial appointment. The difference measure used was an un-weighted sum of absolute differences in age and date of initial care. The maximum allowable difference was three years for age and two years for date of initial care. SAS macros from the Mayo Clinic Division of Biostatistics were used to perform the matching.⁹

The medical charts for these 104 patients (52 refugees, 52 matched non-refugees) were reviewed and the following variables were extracted and tabulated: demographics (marital status, country of nationality), primary risk factor for HIV infection (heterosexual, injection drug use (IDU), men who have sex with men (MSM), other), substance use (any alcohol use, IDU), medical co-morbidities (active TB, latent TB infection (LTBI; defined as a tuberculin skin test ≥ 5 mm with a negative chest X-ray), hepatitis A antibody status, active hepatitis B (defined as a positive hepatitis B surface antigen), hepatitis C antibody status, syphilis (rapid plasma regain (RPR) reactivity), low albumin (defined as albumin < 3.0 g/dl), leukopenia (defined as total white blood cell count $< 3.5 \times 10^9$ /l), thrombocytopenia (defined as platelet count $< 150 \times 10^9$ /l), anemia (defined as hemoglobin < 12.0 g/dl)), baseline HIV data [initial CD4 count, initial HIV plasma viral load (PVL), presence or absence of baseline antiretroviral resistance determined by genotype testing], and clinical care data since care was established at the center [initiation of ARVs, clinical trial enrollment, adherence to scheduled appointments (defined as the percentage of scheduled appointments attended), weight change (defined as the percentage difference in weight between initial weight and most recent recorded weight), and pregnancies among female subjects since establishing care].

Odds ratios (OR), 95% confidence intervals (CI), and associated *p*-values for the observed categorical, dichotomous outcomes (yes/no, positive/negative) were calculated using McNemar tests. In this context, the OR was interpreted as the ratio of the odds of a positive response for a refugee to the odds of a positive response for a non-refugee control conditional on discordance in the covariate between the refugee and control match. Due to the occasional presence of missing outcomes, statistical significance was also calculated using Ekbohm's method that adjusts for missing covariate values.¹⁰ The results from both tests were compared and discussed. Continuous variables were tested using Wilcoxon signed rank

Table 1 Country of nationality

Region of nationality	Refugee <i>n</i> (%)	Non-refugee <i>n</i> (%)	All participants <i>n</i> (%)
Sub-Saharan Africa	49 (94)	3 (6)	52 (50)
Caribbean	1 (2)	11 (21)	12 (12)
Central America	0	2 (4)	2 (2)
South America	0	4 (7)	4 (4)
USA	0	29 (56)	29 (28)
Other	2 (4)	3 (6)	5 (5)

tests, examining whether the median difference between the covariate value of the refugee and matched control differed from zero. Marital status and HIV risk categories were not dichotomous since there were more than two outcome levels; therefore the Fisher's exact test was used to examine demographics and risk factors including substance use variables. All tests were two-sided and *p*-values ≤ 0.05 were considered statistically significant.

The Institutional Review Board of The Miriam Hospital approved the study protocol.

Results

The medical charts of 52 HIV-infected refugees and 52 HIV-infected non-refugees matched for age, gender, and date of initial care were reviewed. Sixty-three percent of the subjects were female. The mean age in the refugee group was 34.2 years (range 21–56 years) and in the non-refugee group was 35.3 years (range 22–58 years). Between the refugees and their non-refugee match, the average absolute difference in age was 1.9 years (range 0–3 years) and the average

absolute difference in date of initiation of HIV care was 92 days (range 0–483 days).

The majority of refugees were from Sub-Saharan Africa (94%), as demonstrated in Table 1. Sixty-seven percent of the refugees were from Liberia with 27% from other Sub-Saharan countries. Interestingly, 44% of the non-refugees were foreign born reflecting a diverse patient population at our center. Demographics, primary risk factor for HIV infection, and substance use history are summarized in Table 2. There were no significant differences in marital status with approximately one-third married in each group. There were significant differences in reported primary HIV risk factor ($p = 0.001$) among the refugees and non-refugees with 81% and 60% reporting heterosexual risk, 0% and 17% reporting male-to-male sex, and 2% and 12% reporting IDU as their primary risk factor, respectively. Refugees were less likely to use alcohol than non-refugees (OR 0.18, 95% CI 0.06–0.52, $p < 0.001$), with 15% of refugees and 40% of non-refugees reporting alcohol use. Similarly, the refugees were less likely to engage in IDU compared to the non-refugees (OR 0.12, 95% CI 0.003–1.0, $p = 0.03$), with 2% of refugees and 13% of non-

Table 2 Summary of demographic characteristics, HIV risk, and substance use by refugee status (*N* = 104)

	Refugee <i>n</i> (%)	Non-refugee <i>n</i> (%)	All <i>n</i> (%)	Fisher's exact test OR ^a (95% CI)	<i>p</i> -Value
Marital status					0.10
Divorced	1 (2)	8 (15)	9 (9)		
Married	18 (35)	16 (31)	34 (33)		
Separated	3 (6)	3 (6)	6 (6)		
Single	21 (40)	22 (42)	43 (41)		
Widowed	6 (12)	2 (4)	8 (8)		
Unknown	3 (6)	1 (2)	4 (4)		
Primary HIV risk category					0.001
Heterosexual	42 (81)	31 (60)	73 (70)		
IDU	1 (2)	6 (12)	7 (7)		
MSM	0 (0)	9 (17)	9 (9)		
Other ^b	5 (10)	3 (6)	8 (8)		
Unknown	4 (8)	3 (6)	7 (7)		
Alcohol				0.18 (0.06–0.52)	<0.001
No	41 (79)	19 (37)	60 (58)		
Yes	8 (15)	21 (40)	29 (28)		
Unknown	3 (6)	12 (23)	15 (14)		
IDU				0.12 (0.003–1.0)	0.03
No	48 (92)	40 (77)	88 (85)		
Yes	1 (2)	7 (13)	8 (8)		
Unknown	3 (6)	5 (10)	8 (8)		

OR, odds ratio; CI, confidence interval; IDU, injection drug use; MSM, men who have sex with men.

^a OR: the ratio of the odds of a positive response for a non-refugee control to the odds of a positive response for a refugee.

^b 'Other' includes perinatal transmission and transmission via blood transfusion or needle stick.

refugees reporting IDU. Information regarding risk factor for HIV infection and substance use was collected from a standardized questionnaire used by our social worker during the initial intake session completed on establishment of care at our center.

Table 3 demonstrates a comparison of co-morbidities reported or determined by laboratory evaluation at the initial clinic visit. There were no significant differences in the number of active TB cases upon initial evaluation with one case among the refugees and three cases among the non-

refugees. Two refugees had a history of active TB prior to relocation. However, 27% of the refugees had LTBI, as determined by TB skin testing. There were no cases of LTBI, nor a history of active TB among the non-refugees (OR infinity, 95% CI 0.92–infinity, adjusted $p < 0.001$). The odds of having hepatitis A antibody reactivity was higher among the refugees (OR 23.0, 95% CI 3.7–947, $p < 0.001$), with 81% of refugees having positive antibody tests versus 38% of non-refugees. Similarly, refugees had a higher odds of having active hepatitis B (OR infinity, 95% CI 2.2–infinity, adjusted

Table 3 Comparison of co-morbidities between refugees and non-refugees at initial visit to the immunology clinic ($N = 104$ unless otherwise noted)

	Refugee n (%)	Non-refugee n (%)	All n (%)	Observed data only ^a		Adjusted for unknown ^b p -Value
				OR ^c (95% CI)	p -Value	
Active TB				0.33 (0.01–4.15)	0.62	0.32
No	49 (94)	46 (88)	95 (91)			
Yes	1 (2)	3 (6)	4 (4)			
Unknown	2 (4)	3 (6)	5 (5)			
Latent TB ($N = 98$)				N/C	0.07	<0.001
Negative	24 (49)	27 (55)	51 (52)			
Positive	13 (27)	0 (0)	13 (13)			
Unknown	12 (24)	22 (45)	34 (35)			
Hepatitis A antibody positive				23.0 (3.73–947)	<0.001	<0.001
Negative	6 (12)	29 (56)	35 (34)			
Positive	42 (81)	20 (38)	62 (60)			
Unknown	4 (8)	3 (6)	7 (7)			
Active hepatitis B				N/C	0.004	0.002
Negative	42 (81)	50 (96)	92 (88)			
Positive	10 (19)	0 (0)	10 (10)			
Unknown	0	2 (4)	2 (2)			
Hepatitis C antibody positive				0.2 (0.0–1.79)	0.22	0.20
Negative	50 (96)	45 (87)	95 (91)			
Positive	2 (4)	5 (10)	7 (7)			
Unknown	0	2 (4)	2 (2)			
Syphilis (RPR)				2.0 (0.29–22.1)	0.68	0.75
Negative	43 (83)	42 (81)	85 (82)			
Positive	4 (8)	3 (6)	7 (7)			
Unknown	5 (10)	7 (13)	12 (12)			
Low albumin				1.25 (0.27–6.3)	1.0	0.77
No	46 (88)	46 (88)	92 (88)			
Yes	6 (12)	5 (10)	11 (11)			
Unknown	0	1 (2)	1 (1)			
Leukopenia				0.57 (0.12–2.25)	0.55	NA
No	46 (88)	43 (83)	89 (86)			
Yes	6 (12)	9 (17)	15 (14)			
Thrombocytopenia				1.5 (0.36–7.23)	0.75	NA
No	46 (88)	48 (92)	94 (90)			
Yes	6 (12)	4 (8)	10 (10)			
Anemia				1.78 (0.74–4.56)	0.23	NA
No	29 (56)	36 (69)	65 (62)			
Yes	23 (44)	16 (31)	39 (38)			

OR, odds ratio; CI, confidence interval; N/C, not calculated; NA, not applicable; TB, tuberculosis; RPR, rapid plasma reagin.

^a McNemar test for paired data.

^b Adjusted p -value using Ekbohm's method.

^c OR: the ratio of the odds of a positive response for a non-refugee control to the odds of a positive response for a refugee.

Table 4 Comparison between refugees and non-refugees with respect to baseline CD4 count and plasma viral load

	Refugee	Non-refugee	All	p-Value ^a
Initial CD4 count, cells/dl (<i>N</i> = 100)				0.51
Median	396	313.5	336.5	
Range	20–1252	2–1176	2–1252	
Initial plasma viral load (log ₁₀)				0.10
Median	4.07	4.32	4.15	
Range	1.72–5.70	2.06–5.88	1.72–5.88	

^a Wilcoxon signed rank test.

$p = 0.002$), with 19% of the refugees and zero non-refugees having active hepatitis B. Hepatitis C antibody reactivity was slightly less common among the refugees (4% vs. 10%) but this was not statistically significant. There were no significant differences in the following baseline laboratory tests among refugees and non-refugees, respectively: RPR reactivity (8%, 6%), hypoalbuminemia (12%, 10%), leukopenia (12%, 17%), thrombocytopenia (12%, 8%), or anemia (44%, 31%).

With respect to baseline HIV clinical variables, the initial median CD4 count and the initial median HIV PVL among the refugees (396 cells/dl, 4.07 log₁₀, respectively) and non-refugees (313.5 cells/dl, 4.32 log₁₀, respectively) were similar although there was a trend toward higher CD4 counts and lower PVLs among the refugees (Table 4). Only one participant, a refugee, had a baseline mutation on genotype testing that revealed possible antiretroviral resistance (V108I mutation).

There were differences between the refugees and the non-refugees in clinical variables after establishing care (Table 5). Refugees were less likely to initiate ARVs by the time the study had been completed (OR 0.37, 95% CI 0.13–

0.92, $p = 0.03$) with 56% of the refugees and 79% of the non-refugees starting ARVs. The odds were lower for refugees to have participated in a clinical study compared to their non-refugee counterparts (OR 0.17, 95% CI 0.02–0.75, $p = 0.02$), with only 6% of the refugees having been enrolled in a clinical trial compared to 25% of the non-refugees. Refugees were less likely to adhere to scheduled appointments compared to non-refugees (median adherence of 75% and 86%, respectively) although this did not reach statistical significance ($p = 0.17$). There were no significant differences in percent weight change since establishing care between the two groups, with an overall median percent weight increase of 3.7 pounds. Similar proportions of females among the refugees and non-refugees had at least one pregnancy during the time the study was conducted (32% and 26%, respectively) which was not statistically different.

Discussion

The HIV-infected refugee population receiving care at our center is largely from Sub-Saharan Africa with the majority of

Table 5 Comparison between refugees and non-refugees with respect to clinical characteristics after establishing care (*N* = 104 unless otherwise noted)

	Refugee	Non-refugee	All	OR ^a (95% CI)	p-Value
Adherence with scheduled appointments, % (<i>N</i> = 96)					0.17 ^b
Median	75%	86%	80%		
Range	0.47–1.0	0.38–1.0	0.38–1.0		
% Weight change (calculated in lbs) since entering care					0.13 ^b
Median	3.8	3.5	3.7		
Range	–10.4–50.5	–16.9–52.3	–16.9–52.3		
HAART use, <i>n</i> (%)				0.37 (0.13–0.92)	0.03 ^c
No	23 (44)	11 (21)	34 (33)		
Yes	29 (56)	41 (79)	70 (67)		
Clinical study enrollment, <i>n</i> (%)				0.17 (0.02–0.75)	0.02 ^c
No	49 (94)	39 (75)	88 (85)		
Yes	3 (6)	13 (25)	16 (15)		
Pregnancy, <i>n</i> (%) (<i>N</i> = 68)				1.29 (0.43–4.06)	0.80 ^c
No	23 (68)	25 (74)	48 (71)		
Yes	11 (32)	9 (26)	20 (29)		

OR, odds ratio; CI, confidence interval; HAART, highly active antiretroviral therapy.

^a OR: the ratio of the odds of a positive response for a non-refugee control to the odds of a positive response for a refugee.

^b Wilcoxon signed rank test.

^c McNemar test for paired data.

refugees coming from Liberia, which is not surprising given the strong historical ties between Liberia and Rhode Island. Interestingly, almost one-half of the non-refugees were foreign born. Through this analysis, we determined that there were significant differences between our refugee and non-refugee populations that are important to consider when planning refugee HIV care, health education, and prevention programs.

The majority of refugees and non-refugees reported heterosexual risk as the primary risk factor for HIV infection, although the proportion was greater among the refugees. There was almost no reported MSM or IDU HIV risk among the refugees, which is similar to the findings of other studies including a recent analysis of HIV-infected African immigrants in Minnesota.^{11,12} When developing HIV counseling, testing, and prevention programs that target refugees and persons from Sub-Saharan countries, it is important to realize that heterosexual transmission may be most prevalent. Education and counseling should be appropriately tailored to heterosexual transmission. Refugees may be offended or react negatively to inquiries of illicit drug use or of male-to-male sex. Care must be taken to approach these questions with sensitivity as drug use and homosexuality often are not discussed openly in many cultures. Providers should complete HIV risk assessment and HIV prevention education in a manner that is culturally acceptable to the refugee population.

There were a number of differences with respect to comorbidities. LTBI and active hepatitis B infection were more common among the refugees. Providers caring for refugees need to have the resources and expertise to treat LTBI and active hepatitis B or have the capacity to refer for appropriate treatment. There is an increased risk of LTBI converting to active TB in persons who are HIV-infected, therefore completion of LTBI treatment is important and referral to a dedicated TB clinic should be considered if available. There was not a significant difference in hepatitis C antibody reactivity among the refugees and non-refugees, which can likely be accounted for by the low number of subjects reporting IDU as their primary risk factor. There was not a significant difference in RPR reactivity and we were not able to successfully compare the presence of other sexually transmitted infections due to lack of data on a significant proportion of subjects. We found no differences in baseline albumin or hematological abnormalities.

The refugees and non-refugees had similar stages of HIV disease upon presentation. Median CD4 counts and PVLs were similar and there was essentially no baseline HIV resistance on genotype testing among either group. However, a smaller proportion of refugees were started on ARVs during the course of the study compared to non-refugees (56% and 79%, respectively). There were several possible reasons for this. In our experience, explaining the indications for ARV treatment and reasons for initiating or postponing ARV therapy to refugees can be challenging. Refugees may not understand why a provider would not begin treatment (based upon a preserved CD4 count) if treatment is effective. The perception that treatment is being withheld can lead to feelings of mistrust. In other instances, refugees who are asymptomatic may feel as though they do not require medicine and may be reluctant to start treatment. Refugees may have only experienced taking medicine when

ill, not for the prevention of illness, including opportunistic infections.

Issues surrounding HIV treatment can be difficult to effectively communicate. Success often requires multiple explanations provided over several visits that occur with the aid of translators and cultural interpreters. The medical experiences of refugees and their perception of healthcare are predictably dissimilar from those of the provider, and cultural differences play an important role. For many refugees, healthcare experiences may be limited to interactions with traditional healers only. Challenges in communication surrounding the use of ARVs likely contributed to fewer refugees initiating HIV treatment during the course of this study compared to non-refugees. At our center, ARV therapy is available to all patients through the Rhode Island AIDS Drug Assistance Program, so access to medication cannot account for this difference.

Refugees were less likely to enroll in a clinical study compared to non-refugees. Clinical studies included trials conducted by the AIDS Clinical Trials Group. There were no studies being conducted during this time that excluded enrollment of refugees based on their refugee status alone. Enrollment in clinical studies was not possible if the patient could not speak English or Spanish, which may have influenced our findings. However, many of the Liberian refugees were English speaking and approximately one-half of the non-refugees were foreign born, so this limitation likely did not account for the entire difference observed. We hypothesize that decreased enrollment among the refugees can be attributed to factors that similarly led to decreased utilization of ARVs. Effectively communicating the objectives of a clinical study to a refugee was challenging given cultural differences, and refugees often had a limited understanding of, or fear of, human research. In addition, enrollment would have required the refugee to disclose their HIV-positive status to additional healthcare workers and refugees often tried to avoid disclosure whenever possible. Strategies to increase enrollment of refugees into clinical studies need to be developed.

The proportion of refugees and non-refugees who became pregnant since care was established was similar (32% and 26%, respectively), which was surprising since there was a perception that more pregnancies occurred among refugee patients. This perception was likely a consequence of pregnancies occurring within different contexts between refugees and non-refugees. Refugee pregnancies often occurred in the absence of pre-pregnancy planning, while non-refugee pregnancies were typically planned in conjunction with the HIV provider and with the use of antiretroviral therapy. Unplanned pregnancies among refugees created the need for urgent clinical evaluations, initiation of ARVs, and social work assistance thus creating a sense of 'crisis management' among the providers. Pregnancies among HIV-infected refugees deserves further research including examination of motivations to become pregnant, circumstances that lead to pregnancy such as inability to negotiate condom usage with sexual partners, pre-natal care, use of ARVs, and pregnancy outcomes.

There were limitations to this study. Data collection was retrospective and limited to a medical chart review only. Our refugee population was homogeneous with the majority of refugees coming from Liberia and other Sub-Saharan coun-

tries, therefore, these results may not apply to other HIV-infected refugee populations. Refugees from Asia and Eastern Europe, for instance, may have different co-morbidities and challenges since HIV transmission in these parts of the world is predominantly through injection drug use. Further investigation into mental health disorders and pregnancy among refugees and non-refugees was not possible given the limitations of the study design.

The HIV-infected refugee population in the USA will continue to grow and the unique needs of this population require attention. Further investigation is needed in the following areas: HIV treatment outcomes among refugees, HIV diversity and the subsequent impact on treatment and the emergence of ARV resistance, investigation into social and cultural factors that predict successful engagement in longitudinal HIV care, preferred ARV regimens and issues of ARV adherence and toxicity, issues surrounding pregnancy and pregnancy outcomes, and further investigation into co-morbidities with particular attention to mental health disorders. Further research will help create multidisciplinary comprehensive care programs that are capable of delivering high-quality care to this disenfranchised and vulnerable population.

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